Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Maraviroc (MVC, Selzentry) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Oral Solution: 20 mg/mL
Tablets: 25 mg, 75 mg, 150 mg, 300 mg

Dosing Recommendations

Neonate and Infant Dose:

- Maraviroc (MVC) is not approved by the Food and Drug Administration (FDA) for use in neonates or infants.

Pediatric Dose:

- MVC is approved by the FDA for use in ART-experienced children aged ≥2 years and weighing ≥10 kg who have CCR5-tropic HIV-1.

Recommended Maraviroc Dose for Treatment-Experienced Children Aged ≥2 Years and Weighing ≥10 kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when MVC is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs) except tipranavir/ritonavir (TPV/r)			
10 kg to <20 kg	50 mg	2.5 mL	Two 25-mg tablets
20 kg to <30 kg	75 mg to 80 mg	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
≥40 kg	150 mg	7.5 mL	One 150-mg tablet
Recommended doses when MVC is given with non-interacting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (T-20), TPV/r, and raltegravir (RAL)			
10 kg to <20 kg	**Not recommended.** Data are insufficient to make dosing recommendations for children weighing <30 kg and receiving non-interacting medications.		
20 kg to <30 kg			
30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
≥40 kg	300 mg	15 mL	One 300-mg tablet
Recommended doses when MVC is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz (EFV) and etravirine (ETR)			
Children in all weight bands	**Not recommended.** Data are insufficient to make dosing recommendations.		

Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

Special Instructions

- MVC is recommended for use in patients who only have CCR5-tropic HIV-1. Before using MVC, conduct testing with an HIV tropism assay (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines) to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use MVC if CXCR4-tropic or mixed/dual-tropic HIV is present.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism/Elimination

- MVC is a substrate of CYP3A4. If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of MVC should be adjusted accordingly.

Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering MVC to patients with hepatic impairment; MVC concentrations may be increased in these patients.

Recommended Maraviroc Dose for Adults: Tablets

When Coadministered With:	Dose
Potent CYP3A inhibitors (with or without a potent CYP3A inducer), including all PIs except TPV/r	150 mg twice daily
Non-interacting concomitant medications, including NRTIs, T-20, TPV/r, NVP, and RAL	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor), including EFV and ETR	600 mg twice daily

Maraviroc Dosing in Patients with Renal Impairment:

- There are no data to recommend specific doses of MVC for pediatric patients with mild or moderate renal impairment. MVC is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease who are on regular hemodialysis and who are receiving potent CYP3A inhibitors.
- Refer to the manufacturer's prescribing information for the appropriate doses to use in adult patients with renal impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Absorption:* Absorption of maraviroc (MVC) is slightly reduced with ingestion of a high-fat meal. There were no food restrictions in the adult trials (which used the tablet formulation) or in the pediatric trial (which used both the tablet and oral solution formulations) that demonstrated the efficacy, antiviral activity, and safety of MVC. Therefore, MVC can be given with or without food.
- *Metabolism:* MVC is a cytochrome P450 (CYP) 3A and p-glycoprotein (P-gp) substrate and requires dose adjustments when administered with medications that modulate CYP3A or P-gp. A patient's medication profile should be carefully reviewed for potential drug interactions before MVC is administered; recommended MVC doses are based on concomitant medications and their anticipated effect on MVC metabolism.

Major Toxicities

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, vomiting, diarrhea, and headache. Dizziness occurred in 12.2% of adults but only 3.2% of children when MVC was administered twice daily.
- *Less common (more severe):* Hepatotoxicity has been reported; some cases were preceded by evidence of a systemic allergic reaction (including pruritic rash, eosinophilia, or elevated levels of immunoglobulin). Serious adverse events (AEs) occurred in <2% of MVC-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance

An HIV tropism assay should be performed before MVC is administered to a patient. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Use

Approval

MVC is approved by the Food and Drug Administration for use in treatment-experienced children aged ≥2 years and weighing ≥10 kg who have CCR5-tropic HIV-1.[1] A study of MVC dosing in neonates and infants is currently underway (*ClinicalTrials.gov* identifier NCT02778204). Preliminary data have been presented.[2]

Pharmacokinetics and Efficacy

The pharmacokinetics, safety, and efficacy of MVC were examined in an international dose-finding and efficacy study (A4001031) that involved treatment-experienced children aged 2 years to <18 years and weighing ≥10 kg who had plasma HIV RNA >1,000 copies/mL. Fifty-one percent of the 103 children who participated in the study had HIV-1 subtype C, 25% had subtype B, and 23% had other subtypes.

In this trial, the MVC dose was based on body surface area and the composition of the patient's optimized background therapy. Most participants (90 of 103 participants, or 87%) received MVC in combination with potent CYP3A inhibitors, while 10 participants received MVC with noninteracting medications and only three participants received MVC with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean $C_{average}$ of >100 ng/mL) was achieved with both the tablet and oral solution formulations of MVC.[3]

From a mean baseline plasma HIV RNA concentration of 4.4 $\log_{10}$ copies/mL, a decrease of ≥1.5 $\log_{10}$ occurred in all four age-based cohorts. Only two participants discontinued the study due to AEs. The most common MVC-related AEs through 48 weeks were diarrhea (which occurred in 20.3% of participants), vomiting (19.8%), and upper respiratory infections (16.2%). At Week 48, 48% of participants had HIV RNA <48 copies/mL.[3] The absolute CD4 T lymphocyte cell count and percentage increased in all four subgroups of the study, with overall median increases of 192 cells/mm^3 (interquartile range [IQR] 92–352 cells/mm^3) and 4% (IQR 1% to 8%), respectively.

References

1. Maraviroc [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022128s018,208984s001lbl.pdf.
2. Rosebush JC, Best B, Chadwick E, et al. Maraviroc safety & pharmacokinetics in HIV-exposed neonates. Abstract 842. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, Massachusetts. Available at: https://www.croiconference.org/sessions/maraviroc-safety-pharmacokinetics-hiv-exposed-neonates.
3. Giaquinto C, Mawela MP, Chokephaibulkit K, et al. Pharmacokinetics, safety and efficacy of maraviroc in treatment-experienced pediatric patients infected with CCR5-tropic HIV-1. *Pediatr Infect Dis J*. 2018;37(5):459-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29023357.